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Therapeutic plasma exchange in adults with severe COVID-19 infection

Faryal Khamis[a,*], Ibrahim Al-Zakwani[b], Sabria Al Hashmi[c], Samata Al Dowaiki[a], Maher Al Bahrani[d], Nenad Pandak[a], Huda Al Khalili[d], Ziad Memish[e]

[a] Infection Diseases Unit, Royal Hospital, Muscat, Oman
[b] Department of Pharmacology & Clinical Pharmacy, College of Medicine & Clinical Pharmacy, Sultan Qaboos University, Muscat, Oman
[c] Department of Clinical Hematology, Royal Hospital, Muscat, Oman
[d] Department of Anesthesia and Critical Care, Royal Hospital, Muscat, Oman
[e] Research and Innovative Centre, King Saud Medical City, Ministry of Health, Riyadh, Saudi Arabia

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ABSTRACT

Objective: To evaluate the therapeutic use of plasma exchange in COVID-19 patients compared to controls.
Methods: A case series of critically ill adult men and non-pregnant women, ≥18 years of age, with laboratory-confirmed COVID-19, was studied at the Royal Hospital, Oman, from April 17 to May 11, 2020. Therapeutic plasma exchange (TPE) was performed on patients admitted to the intensive care unit (ICU) with confirmed or imminent acute respiratory distress syndrome (ARDS) or severe pneumonia. The analysis was performed using univariate statistics.
Results: A total of 31 COVID-19 patients were included with an overall mean age of 51 ± 15 years (range: 27–76 years); 90% (n = 28) were males, and 35% (n = 11) of the patients had TPE as a mode of treatment. The TPE group was associated with higher extubation rates than the non-TPE cohort (73% *versus* 20%; $p = 0.018$). Additionally, patients on TPE had a lower 14 days (0 *versus* 35%; $p = 0.033$) and 28 days (0 *versus* 35%; $p = 0.033$) post plasma exchange mortality compared to patients not on TPE. However, all-cause mortality was only marginally lower in the TPE group compared to the non-TPE group (9.1% *versus* 45%; $p = 0.055$; *power* = 66%). Laboratory and ventilatory parameters also improved post TPE (n = 11).
Conclusions: The use of TPE in severe COVID-19 patients has been associated with improved outcomes, however, randomized controlled clinical trials are warranted to draw final, conclusive findings.

Introduction

The novel coronavirus ("SARS-CoV-2") pandemic continues to spread globally with an estimated 7,930,989 cases and 433,783 (Wikipedia - COVID-19 pandemic by country and territory, 2020) deaths (as of June 15, 2020) without available effective treatment or vaccine. In search of the cure, several randomized controlled clinical trials are in progress (Keith et al., 2020a,b). The SARS-CoV-2 virus infects the respiratory epithelium of the lower airways, causing widespread damage *via* cytopathic effects, resulting in severe inflammation and pneumonitis. It is estimated that 13.8% of cases are severe, and 6.1% are critical (WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), 2020) that manifest as acute respiratory distress syndrome (ARDS), sepsis and /or multiorgan failure. The response to fulminant COVID-19 infection is characterized by excessive immune dysregulation (cytokine storm), inflammation, hypercoagulable state, and endothelial dysfunction (Keith et al., 2020a,b; Chang, 2019). Severe COVID-19 disease has been associated with lymphopenia and high levels of ferritin, C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer and interleukin-6 (IL-6) (Xu et al., 2020).

Recently, convalescent plasma containing protective antibodies, donated from survivors of COVID-19 infection, has been shown as a promising and safe treatment (Joyner et al., 2020). Similarly, therapeutic plasma exchange (TPE), which is not a novel therapy,

* Corresponding author at: Department of Infectious Diseases, The Royal Hospital, Muscat, Oman.
E-mail address: khami001@gmail.com (F. Khamis).

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has been used in several studies for the management of severe infections such as 2009 HIN1 influenza A, sepsis and multiorgan failure with a trend towards improved survival (Knaup et al., 2018; Busund et al., 2002; Rimmer et al., 2014; Patel et al., 2011; Keith et al., 2020a,b). TPE has been proposed as a possible supportive treatment for severe COVID-19 infection and has been effective in a few case reports (Shi et al., 2020; Zhang et al., 2020).

We report here the results of TPE as a supportive/adjunct therapy for the management of COVID-19 ARDS and severe pneumonia.

Methods

The study was conducted at the Royal Hospital, a tertiary care hospital in Muscat, Oman, from April 17, 2020, to May 11, 2020. TPE was given after seven and up to 14 days of illness to adult patients, ≥18 years of age, with laboratory-confirmed SARS-CoV-2 infection who were admitted to the intensive care unit (ICU) with confirmed or imminent respiratory failure and any one of the following conditions (ARDS Definition Task Force et al., 2012):

1 ARDS was defined as acute-onset hypoxemia (the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen [Pao2:Fio2], <300) with >50% bilateral pulmonary opacities on chest imaging within 24–48 h that were not fully explained by congestive heart failure.
2 Severe pneumonia in adults was defined as fever or suspected respiratory infection plus one of the following: respiratory rate of >30 breaths/ minute, severe respiratory distress, and SpO2 of <93% on room air.
3 Septic shock in adults was defined as persisting hypotension despite volume resuscitation, requiring vasopressors to maintain mean arterial pressure of ≥65 mmHg and serum lactate level of <2 mmol/L.
4 Multiple organ dysfunction syndrome (MODS) was defined as the progressive, potentially reversible dysfunction of two or more organ systems following acute, life-threatening disruption of systemic homeostasis.

We excluded pregnant women, patients with suspected or confirmed pulmonary embolism, and patients with acute coronary syndrome.

The study was approved by the Royal Hospital Research and Ethics Committee *(SRC#36/2020)*, and written informed consent was obtained from the patient or (if intubated) through the health proxy.

Data collected included demographics, baseline characteristics, risk factors, sequential organ failure assessment (SOFA) score, respiratory parameters (FIO2, PEEP, PO2/FIO2) pre plasma exchange (day 0) and post plasma exchange (day 7), laboratory parameters pre-plasma exchange (day 0) and post-plasma exchange (day 7), absolute lymphocytic count (ALC) (CRP, LDH, ferritin, D-dimer, IL-6, PH, and lactate), radiological features and clinical outcomes including ICU length of stay, total length of stay, extubation and mortality rates at day 14 and day 28 post-plasma exchange as well as all-cause mortality. The data were compared with the medical records of 21 patients admitted from April 17 to May 11, 2020, to the ICU with laboratory-confirmed COVID-19 disease who did not receive any form of plasma therapy. The control group received the usual standard of care as per the National Guidelines (Ministry of Health, Oman Human infection with novel coronavirus (COVID-19)-7. Interim guideline for hospitals, primary care and private healthcare, 2020).

The control group was matched for baseline characteristics and severity of illness.

Description of plasma exchange procedure

TPE was performed using the Spectra Optia® Apheresis System (TermuBact, Japan), a standard plasma exchange kit (Catalog number: 502058310220), with citrate dextrose solution, solution A (ACD-A) used as an anticoagulant. Fresh frozen plasma (FFP) was used as a replacement solution. The total volume of plasma to be replaced was calculated as follows: plasma replacement (L) = body weight (kg) × (1/13) × (100-hematocrit). TPE was performed through a standard femoral central venous catheter (12 Fr). Each patient underwent a total of five procedures.

Statistical analysis

Descriptive statistics were used to describe the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analyzed using Pearson's X^2 tests (or Fisher's exact tests for expected cells of <5). For continuous variables, mean and standard deviation were used to summarize the data, while analyses were performed using Student's *t*-test. Abnormally distributed variables were summarized using median and interquartile range and analyzed using the Wilcoxon Mann–Whitney test. Statistical analyses were conducted using STATA version 16.1 (STATA Corporation, College Station, TX, USA).

Table 1
Demographic and clinical characteristics.

Variable, *n (%) unless specified otherwise*	All (N = 31)	Control group (n = 20)	Plasma exchange group (n = 11)	*p*-value
Age, mean ± SD, years	51 ± 15	51 ± 17	50 ± 10	0.931
Male gender	28 (90%)	17 (85%)	11 (100%)	0.535
Obesity	3 (9.7%)	2 (10%)	1 (9.1%)	1.000
Diabetes mellitus	15 (48%)	7 (35%)	8 (73%)	0.066
Hypertension	12 (39%)	6 (30%)	6 (55%)	0.255
Chronic kidney disease	4 (13%)	3 (15%)	1 (9.1%)	1.000
SOFA score, median (IQR)	5 (3–9)	3 (2–6)	6 (3–9)	0.142
ARDS				
No [PaO2/FiO2 - >200]	11 (35%)	10 (50%)	1 (9.1%)	
Moderate [PaO2/FiO2 100-200]	13 (42%)	6 (30%)	7 (64%)	0.083
Severe [PaO2/FiO2 - <100]	7 (23%)	4 (20%)	3 (27%)	
Severe pneumonia	11 (35%)	10 (50%)	1 (9.1%)	0.047
Septic shock (n = 30)	19 (63%)	10 (53%)	9 (82%)	0.140
Multiple Organ Dysfunction	4 (13%)	3 (15%)	1 (9.1%)	1.000
Tocilizumab use	12 (39%)	6 (30%)	6 (55%)	0.179

SD, standard deviation; IQR, interquartile range; ARDS, acute respiratory distress syndrome.
Some of the *p*-values should be interpreted with caution due to small sample size.

Table 2
Clinical outcome characteristics of the study cohort.

Variable, *median (IQ) unless specified otherwise*	All (N = 31)	Control group (n = 20)	Plasma exchange group (n = 11)	*p*-value
ICU LOS	8 (2–14)	6 (1–14)	14 (8–20)	0.028
Total LOS	13 (9–19)	11 (8–15)	19 (9–21)	0.130
Extubated, n (%)				
Not intubated	10 (32%)	9 (45%)	1 (9.1%)	
No	9 (29%)	7 (35%)	2 (18%)	0.018
Yes	12 (39%)	4 (20%)	8 (73%)	
Mortality, n (%)				
Day 14 mortality	7 (23%)	7 (35%)	0	0.033
Day 28 mortality	7 (26%)	7 (35%)	0	0.033
All-cause mortality	10 (32%)	9 (45%)	1 (9.1%)	0.055

IQR, interquartile range; LOS, length of stay; ICU, intensive care unit.

Results

This study enrolled a total of 31 COVID-19 patients with laboratory confirmed SARS-CoV-2 infection with an overall mean age of 51 ± 15 years (range: 27–76 years) and 90% (n = 28) were males. A total of 35% (n = 11) of the patients had TPE as a treatment mode. The three most prevalent comorbidities were diabetes mellitus (48%; n = 15), hypertension (39%; n = 12) and chronic kidney disease (13%; n = 4). Both the TPE and the control groups had similar baseline characteristics and underlying co-morbidities. The overall median sequential organ failure assessment (SOFA) score was 3 (2–6) for the control group and 6 (3–9) for the TPE group. Ninety one percent (n = 10) of the patients in the TPE group had either moderate [PaO2/FiO2 – 200–100] or severe ARDS [PaO2/FiO2 100-200], while 50% (n = 10) in the control had either moderate or severe ARDS. A total of 50% (n = 10) of the patients in the control group presented with severe pneumonia. Sixty-three percent (n = 19) of the patients had septic shock, 82% (n = 9) in TPE group and 53% (n = 10) in the control group, and 13% (n = 4) had MOD, 9.1% (n = 1) in the TPE group and 15% (n = 3) in the control group, respectively. There was a trend for those in the TPE group to have worse SOFA scores and ARDS, however, the *p*-values were not

Table 3
Clinical indexes, laboratory findings and ventilatory parameters before and after plasma exchange.

Characteristic, units	Patient number										
	1	2	3	4	5	6	7	8	9	10	11
SOFA score											
Pre	13	3	6	9	3	9	6	2	5	8	9
Post	13	2	4	6	2	5	4	2	2	6	6
IL-6, pg/mL											
Pre	3415	n/a	n/a	n/a	1179	503	70	32	19	151	210
Post	73	10	57	284	20.5	112	103	9	15	297	5
CRP, mg/L											
Pre	344	70	250	87	49	274	104	227	57	190	187
Post	12	33	27	416	16	26	124	15	40	140	54
D-dimer, ng/mL											
Pre	27	3.45	3.8	1.49	0.41	3.4	4	7.09	0.56	0.6	1.14
Post	3.7	2.01	2.14	2.09	1.48	1.97	4.9	2.7	1.3	0.95	0.89
Lymphocyte, $x10^9$/L											
Pre	0.6	1.9	0.7	0.8	11 (CLL)	1	0.9	1.2	1.2	0.8	0.6
Post	1.2	2.4	1.2	2.2	13 (CLL)	2.2	1.3	1.7	3	0.7	0.6
Ferritin, ng/mL											
Pre	1924	1178	554	1554	1072	1694	1274	381	937	2329	221
Post	629	339	1088	416	362	661	494	429	411	760	143
$PaO2_2$/FiO2 ratio											
Pre	98	153	156	127	176	134	114	NI	137	118	121
Post	138	240	195	240	238	240	265	NI	188	136	166
FiO2, mmHg											
Pre	75	50	50	50	45	55	50	NI	40	50	60
Post	60	Extub	40	40	Extub	40	40	NI	Extub	60	65
PEEP, cm H_2O											
Pre	16	10	12	17	10	12	12	NI	8	12	12
Post	16	Extub	6	7	Extub	6	8	NI	Extub	14	12

NI, not intubated; IL-6, interleukin 6; CRP, C-reactive protein; CLL, chronic lymphocytic leukemia; FiO2, fraction of inspired oxygen; Extub, extubated; PEEP, positive end-expiratory pressure; H_2O, water.

statistically significant. Those on plasma exchange were less likely to be diagnosed with severe pneumonia than those not on plasma exchange (9.1% *versus* 50%; $p = 0.047$). Table 1

Table 2 outlines the clinical outcome characteristics of the cohort stratified by TPE. Those on plasma exchange were associated with longer ICU length of stay than those that were not on plasma exchange (14 *versus* 6 days; $p = 0.028$), as they were more seriously ill. Additionally, those on TPE were also more likely to be extubated than those not on plasma exchange (73% *versus* 20%; $p = 0.018$). Furthermore, patients on TPE had a lower 14 days (0 *versus* 35%; $p = 0.033$) and 28 days (0 *versus* 35%; $p = 0.033$) mortality compared to patients not on TPE. However, all-cause mortality was only marginally lower in the plasma exchange group than those not on plasma exchange (9.1% *versus* 45%; $p = 0.055$; *power* = 66%).

Clinical indexes, laboratory findings, and ventilatory parameters before and after plasma exchange are presented in Table 3. Those on TPE generally showed reductions in SOFA scores, IL-6, CRP, D-dimer, and ferritin levels.

Discussion

The novel coronavirus (SAR-CoV-2) has generated worldwide attention due to its impact on global health. Presently, there are no definitive treatments for COVID-19 infection, and current management strategies focus on supportive care, infection control, and investigational therapies. Morbidity and mortality from COVID-19 infection have been linked to certain risk factors that include: age, prior lung disease, diabetes mellitus, cardiac disease, hypertension, and stroke (Chen et al., 2020; Chen et al., 2019; Khamis et al., 2020). The most prevalent risk factors in our patients were diabetes mellitus, hypertension, and chronic renal disease.

Nearly all of the patients in the plasma group (10/11) presented with moderate to severe ARDS, while severe pneumonia was the main presentation in the control group. In comparison to the control group, the clinical outcomes were favorable in terms of extubation and mortality benefit with TPE, and the effect on the mortality extended up to 28 days (0 *versus* 35% mortality, $p = 0.033$). There was also a tendency towards improvement in overall all-cause mortality; however, the sample size was small as denoted by the study's statistical power of only 66%.

The leading causes of death in patients with COVID-19 infection are ARDS and cytokine storm syndrome (Felsenstein et al., 2020; Huang et al., 2020; Qin et al., 2020). Additionally, 50% of patients presenting with cytokine storm syndrome usually develop ARDS (Chen et al., 2019); thus, early recognition and control of a dysregulated immune reaction are essential. In severe COVID-19 infection, TPE removes toxins and deleterious inflammatory cytokines such as IL-1, IL-6, granulocyte-colony stimulating factor, tumor necrosis factor, and other inflammatory parameters. These inflammatory mediators can trigger a cytokine storm-mediated immune injury to the different target organs, resulting in capillary leak syndrome, progressive lung injury, respiratory failure and ARDS, shock, acute kidney injury, and liver impairment (Seguin et al., 2016).

Simultaneous replacement with normal or convalescent plasma helps to improve hypercoagulable state, reduce cytokine response, and replaces ADAMTS13 enzyme (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13). TPE's effect on clinical and laboratory parameters was instantly observed following the completion of the five cycles (day 7). This included improvement in SOFA scores, an increase in the ALC, and reduction in all inflammatory parameters such as CRP, D-dimer, ferritin, and IL-6. This effect has also been reported elsewhere (Shi et al., 2020; Zhang et al., 2020).

Just over half of our patients in the TPE group and one third in the control group received the IL-6 inhibitor, tocilizumab, after plasma exchange, and this might have additionally contributed to the decrease in the cytokine storm. However, in a study by Xu et al. the reduction in the inflammatory markers was instant even before receiving the IL-6 inhibitor (Xu et al., 2020).

The use of TPE in the treatment of severe COVID-19 infection has shown some positive results; however, the benefit has been limited in macrophage activation syndrome or sepsis complicated with MODS (Ma et al., 2020). Theoretically, TPE could also remove the formed SARS-CoV-2 antibodies in addition to the “harmful” dysregulated inflammatory mediators, but it remains unclear if there is an antibody response during the cytokine storm or it develops subsequently. In this regard, the current recommendation of the American Plasma Exchange Association is as follows "the effectiveness of plasma exchange has not yet been determined and should be individually selected" (Winters, 2012).

In the implementation of plasma exchange, the key factor in its success is to start TPE in the early stages of COVID-19 inflammation, when proinflammatory cytokines are probably high (Yang et al., 2020). In COVID-19 patients, it has been reported that the inflammatory cytokines released with severe diseases, including IL-6, were significantly higher around seven to 14 days after the onset of the illness (Wan et al., 2020). Thus, early initiation of TPE treatment within this time frame could be associated with better outcomes. In our patients, TPE was initiated from seven days and up to 14 days of illness.

It is also necessary to administer TPE for the correct duration and volume, to monitor the potential drug removal of specific therapies such as immunomodulating agents and to practice the proper infection prevention and control measures. TPE is a tolerable procedure by most patients without adverse events; however, the procedure can be a challenge to perform in COVID-19 patients who are placed in a prone position. Earlier studies of the use of plasma exchange in sepsis have shown that both the timing and disease severity are important for the beneficial effect of TPE (Yang et al., 2020). We routinely performed five TPEs daily and noted that respiratory improvements were only seen after completing the therapy on day 7. Recognized adverse events related to TPE include allergic reactions, hypotension, hypocalcemia, and line-related infections. All patients in this case study tolerated TPE except for one hypotension episode, which resolved after normal saline bolus and hydrocortisone injection and did not recur with subsequent procedures.

We note that this single-center small trial is not without limitations. Although patients might have improved naturally, the laboratory and ventilatory changes before and after plasma exchange are encouraging for the TPE group. The use of the IL-6 antagonist, tocilizumab, could have contributed to TPE's beneficial effects. The current study is a case series with a small number of patients; a larger well-powered randomized clinical trial is warranted to confirm the beneficial outcomes of TPE.

Conclusion

This single-center, case series study on the use of TPE in the management of COVID-19 infection has demonstrated encouraging results and supports the need for further investigations. Based on our experience, TPE should be utilized earlier in critically ill patients with MODS and ARDS within seven to 14 days of illness onset. TPE shows promise; however, randomized clinical trials are warranted to draw final, conclusive findings.

Conflict of interest

None.

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Ethical approval

Ethical approval has been obtained by the Scientific Research Committee at the Royal Hospital *(SRC#36/2020)*, Ministry of Health, Oman.

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